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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,481	01/20/2004	Nozer M. Mehta	P/546-280	2921

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,481	MEHTA ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060713*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claim 64 as set forth in the listing of claims filed July 13, 2006 is in improper format under 37 CFR 1.121(c)(4). Claim text shall not be presented when canceling a claim. In any future amendment to the claims, the claim format of this canceled claim must be corrected.

2. The effective filing date of instant claims 1-63 is January 21, 2003, the filing date of provisional application 60/441,856. Instant claims 1-63 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed subject matter.

The effective filing date of instant claim 65 is January 20, 2004, the filing date of the instant application. Instant claim 65 is not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/441,856 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose general pharmaceutical compositions for oral delivery in which the PTH 1-34-OH are not amidated.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 45-48, 50, 51, 54, 56, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern et al (U.S. Patent No. 5,912,014). Stern et al teach oral administration of salmon calcitonin using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. The salmon calcitonin is made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 4, line 63 - column 9, line 10, and claims 1-32. Note that the instant method claims, in contrast to the instant composition claims, do not require the peptide

agent to be amidated at a site that is not naturally amidated.

5. Claims 45-47, 50, 51, 54, 56, 61, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern et al (U.S. Patent No. 6,086,918). Stern et al teach oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, and lhrf using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. See, e.g., column 6, line 1 - column 12, line 10, and claims 1-55. Salmon calcitonin and lhrf (which is the same as LHRH) are amidated at their C-termini in their naturally-occurring forms. Note that the instant method claims, in contrast to the instant composition claims, do not require the peptide agent to be amidated at a site that is not naturally amidated.

6. Claims 1-8, 12-47, 49-51, 54-60, 62, 63, and 65 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) as applied against claims 45-47, 50, 51, 54, 56, 61, and 63 above, and further in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742). Stern et al do not teach peptides which are amidated GLP-1 analogs, amidated insulin analogs, or amidated PTH analogs. Habener teaches GLP-1 analogs which are amidated. See, e.g., claims 1 and 4. Balschmidt et al teach insulin in which the carboxylic acid groups present in the sidechains at residues A4, A17, B13, and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. See, e.g., column 2, lines 5-8 and 49-53. Barbier et al teach the human parathyroid hormone derivatives hPTH(1-34)-OH and hPTH(1-31)NH_2. See, e.g., column 2, lines 26-44. The European Patent Application '201 teaches the human parathyroid hormone

derivative hPTH(1-34)NH_2. See, e.g., column 3, lines 31-36. Neiss et al teach salmon calcitonin amidated at locations which are not naturally amidated and which have extended duration of activity. See, e.g., column 1, lines 42-44, and claims 1 and 2. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al in the oral administration compositions of Stern et al because the oral administration compositions of Stern et al have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Balschmidt et al, Barbier, the European Patent Application '201, and Neiss et al because oral administration is easier for the patient. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

7. Claims 45-48, 50-54, 56, 61, and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 02/043767. The WO Patent Application '767 teaches oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, lhrf, and GLP-1 linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating. See, e.g., page 17, lines 13-22, page 18, lines 10-27, page 20, lines 11-29, and claims 1-57. Salmon calcitonin and lhrf (which is the same as LHRH) are amidated at their C-termini in their naturally-occurring forms. Note that the instant method claims, in contrast to the instant composition claims, do not require the peptide agent to be amidated at a site that is not naturally amidated. [Note that the WO Patent Application '767 does

not designate the US, and therefore is not available as prior art under 35 U.S.C. 102(e).]

8. Claims 1-47, 49-60, 62, 63, and 65 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 as applied in the above rejection of claims 45-48, 50-54, 56, 61, and 63, and further in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742). The WO Patent Application '767 does not teach peptides which are amidated GLP-1 analogs, amidated insulin analogs, or amidated PTH analogs. Habener teaches GLP-1 analogs which are amidated. See, e.g., claims 1 and 4. Balschmidt et al teach insulin in which the carboxylic acid groups present in the sidechains at residues A4, A17, B13, and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. See, e.g., column 2, lines 5-8 and 49-53. Barbier et al teach the human parathyroid hormone derivatives hPTH(1-34)-OH and hPTH(1-31)NH_2. See, e.g., column 2, lines 26-44. The European Patent Application '201 teaches the human parathyroid hormone derivative hPTH(1-34)NH_2. See, e.g., column 3, lines 31-36. Neiss et al teach salmon calcitonin amidated at locations which are not naturally amidated and which have extended duration of activity. See, e.g., column 1, lines 42-44, and claims 1 and 2. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al in the oral administration compositions of the WO Patent Application '767 because the oral administration compositions have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, and Neiss et al because oral

administration is easier for the patient. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

9. Claims 1, 6, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Balschmidt et al (U.S. Patent No. 5,157,021). Balschmidt et al teach pharmaceutical compositions comprising insulin in which the carboxylic acid groups present in the sidechains at residues A4, A17, B13, and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. See, e.g., column 2, lines 5-8 and 49-53; column 3, line 64 - column 4, line 3; and claims 1-16. Note that an intended use limitation, e.g., "for oral delivery", does not impart patentability to product claims where the product is otherwise anticipated by the prior art.

10. Claims 1, 4, 5, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Habener (U.S. Patent No. 5,120,712). Habener teaches pharmaceutical compositions comprising GLP-1 analogs which are amidated at the C-terminus. See, e.g., column 4, lines 14-29, and claims 1, 4, 5, and 7. Note that an intended use limitation, e.g., "for oral delivery", does not impart patentability to product claims where the product is otherwise anticipated by the prior art. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

11. Claims 1, 4, 5, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Barbier et al (U.S. Patent No. 6,110,892). Barbier et al teach pharmaceutical compositions comprising hPTH(1-31)NH_2. See, e.g., column 9, lines 25-46. Note that an intended use limitation, e.g., "for oral delivery", does not impart patentability to product claims where the

product is otherwise anticipated by the prior art. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

12. Claims 1, 4, 5, 40, 42, 45, 47, 58, and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Peri et al (U.S. Patent Application Publication 2004/0023882). Peri et al teach pharmaceutical compositions comprising hPTH(1-34) amidated at its C-terminus, including hPTH(1-34)NH_2. The compositions can be administered orally. See, e.g., paragraph [0064] and claims 1-2. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

The subject matter disclosed by Peri et al and relied upon in the rejection is also disclosed in the provisional application, 60/378,082, upon which Peri et al claim priority under 35 U.S.C. 119(e). See, e.g., page 10, line 22, and claims 1 and 2 of the provisional application. Accordingly, Peri et al is available as prior art against the instant claims under 35 U.S.C. 102(e).

13. Applicant's arguments filed July 13, 2006 have been fully considered but they are not persuasive.

The rejection over Stern et al (U.S. Patent No. 5,912,014) is maintained. Applicants contend that Stern et al '014 discloses a completely different methodology for increasing bioavailability than is claimed by Applicants. The examiner does not agree. Stern et al '014 teaches the only two positive process steps recited in instant claim 45, i.e. Stern et al '014 amidates the salmon calcitonin and orally administers it. While Stern et al '014 might teach additional steps for increasing oral bioavailability, e.g., the use of pH-lowering agents,

absorption enhancers, and enteric coatings, such steps are not excluded by Applicants' claim language, which uses "comprising" language. In any event, these additional steps of Stern et al '014 are the subject matter of Applicants' dependent claims, e.g., claims 46, 51, and 54, and so the examiner does not agree that Stern et al '014 teaches a "completely different methodology" than is claimed by Applicants. Applicants also point out that salmon calcitonin is naturally amidated. However, the rejected claims do not require that the peptide be amidated at a location that is not naturally amidated. Patentability must be based upon claimed, not unclaimed, differences over the prior art. Applicants' comparison of Stern et al '014 with the limitations of claim 1 is irrelevant to the rejection of record, because Stern et al '014 is not applied against claim 1.

The anticipation rejections over Stern et al (U.S. Patent No. 6,086,918) and over the WO Patent Application 02/043767 are maintained for essentially the same reasons set forth above with respect to Stern et al '014. Note that because Stern et al '918 and the WO Patent Application 02/043767 teach salmon calcitonin and lhrf, two naturally amidated peptides, inherently there must have been an amidating step whereby the amidated peptides were formed. There is no "intent" requirement for a rejection under 35 U.S.C. 102, i.e. a prior art reference does not have to disclose or recognize Applicants' intended purpose or Applicants' intended results in order to anticipate a claim. See MPEP 2112.

The anticipation rejection over Balschmidt et al (U.S. Patent No. 5,157,021) is maintained. The aqueous solutions taught by Balschmidt et al are capable of being administered orally, i.e. they can be swallowed. Applicants have not demonstrated or argued that the "adapted" language requires a particular structure which distinguishes over the solutions of

Balschmidt et al. See MPEP 2111.04. Rather, Applicants still appear to be arguing a difference in intended use, which does not distinguish over a reference which otherwise anticipates the claimed composition.

The anticipation rejections over Habener (U.S. Patent No. 5,120,712) and over Barbier et al (U.S. Patent No. 6,110,892) are maintained for essentially the same reasons set forth above with respect to Balschmidt et al.

The anticipation rejection of the composition claims over Peri et al (U.S. Patent Application Publication 2004/0023882) is maintained. Applicants contend that the C-terminal end of the hPTH(1-34) of Peri et al is a location where amidation naturally occurs, and therefore this peptide is excluded from the scope of Applicants' claims. However, at page 16, lines 1-10, and Example 3 of the specification and at claim 42, Applicants exemplify amidated PTH(1-34) as constituting an amidated peptide according to the invention. The anticipation rejection of the method claims over Peri et al is maintained for essentially the same reasons set forth above with respect to Stern et al '014, Stern et al '918, and the WO Patent Application '767.

The obviousness rejection based upon Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742) is maintained. Because the references are applied in combination under 35 U.S.C. 103, it is irrelevant that the individual references may or may not suggest Applicants' claims. See MPEP 2145(IV).

With respect to the European Patent Application '201, Applicants contend that there is no motivation or suggestion to combine this reference with Stern et al '918. The examiner does not

agree. Stern et al '018's oral administration compositions are disclosed to be useful for administering any therapeutic peptide, including parathyroid hormone (see, e.g., column 5, lines 55-67, and column 6, line 5). The European Patent Application '201 discloses a parathyroid hormone derivative, hPTH(1-34)NH_2, which is useful for preventing or treating thrombocytopenia. The European Patent Application '201 does not disclose oral administration, but is not limited to any particular method of administration (see, e.g., column 4, lines 36-37). Note that the disclosure of a reference is not limited to the reference's preferred embodiments. See MPEP 2123. It would have been obvious to administer the hPTH(1-34)NH_2 of the European Patent Application '201 using the oral administration compositions of Stern et al '018, because Stern et al '018 is not limited to any particular peptide, and hPTH(1-34)NH_2 is closely related to the PTH which Stern et al '018 disclose can be usefully administered with the oral administration compositions; and because European Patent Application '201 is not limited to any particular method of administration, and oral administration of hPTH(1-34)NH_2 would have the benefit of being easier for the patient. The hPTH(1-34)NH_2 of the European Patent Application '201, when administered using the oral administration compositions of Stern et al '018, would have been expected to have enhanced bioavailability in view of Stern et al '018's characterizations of their compositions (see, e.g., the Abstract). There is no evidence of record that Applicants' claimed compositions possess bioavailability which would not have been expected in view of Stern et al '018.

With respect to Neiss et al (U.S. Patent No. 4,804,742), Applicants contend that Neiss et al do not teach "amidated" calcitonin analogs as claimed by Applicants, and cite to a website definition of "amidation". However, this definition can not be accepted because it contradicts

Applicants' use of the term "amidated" throughout the specification and claims. Note, for example, that Applicants claim compositions comprising peptides containing an "amidated side chain". Such peptides can not be formed by "the posttranslational conversion of C-terminal glycine-extended peptides to C-terminal alpha-amidated peptide". Also, Applicants state at page 23, lines 14-16, that amidation can be accomplished by chemical means. Accordingly, the definition cited by Applicants can not be relied upon to distinguish over Neiss et al. The examiner also does not agree that "amidated" and "amide" have different meanings. Note that Applicants use the terms interchangeably, e.g., even Applicants' preferred glycine extension and posttranslation conversion results in a "C-terminal amide group" (emphasis added - see e.g., claim 5). The examiner agrees that Neiss et al's acylation will not result in a calcitonin analog with a C-terminal NH_2 group. However, only certain of the dependent claims (e.g., claim 4) require amidation at the C-terminal end of the peptide. Neiss et al's acylation will result in the formation of an amide group between the amino group of the sidechain and the carboxyl group of the fatty acid, i.e. will result in an amidated calcitonin analog. Finally, the combination of Stern et al '018 and Neiss et al do suggest improved oral bioavailability for the resultant compositions - see, e.g., the Abstract of Stern et al '018. There is no evidence of record that Applicants' claimed compositions possess bioavailability which would not have been expected in view of Stern et al '018. The examiner has reviewed Example 1 of Applicants' specification for evidence of unexpected results. However, the calcitonin tested in this example is amidated at the location which is naturally amidated, i.e. is amidated at the C-terminus. Further, this amidated calcitonin is not compared with non-amidated calcitonin, but rather is compared with calcitonin which has been extended at its C-terminus with a glycine residue. Accordingly, the

example tests an amidated peptide not embraced within the scope of the composition claims, and does not demonstrate the effects of amidation but rather demonstrates the effects of removing a CH_2COOH group from sCT-gly.

The examiner agrees that Stern et al '018 in combination with Neiss et al do not suggest Applicants' claim 65.

The obviousness rejection based upon the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742) is maintained for reasons analogous to those set forth above.

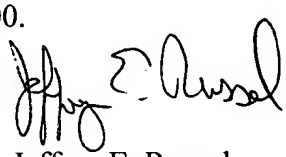
14. The references crossed off of the Information Disclosure Statement filed July 13, 2006 are duplicate citations.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

November 4, 2006